Marked-Up Copy of Amended Specification and Claim

NOTE: Changes are marked by brackets and bold text.

Paragraph 1: Transporters are generally classified by structure and the type of mode of action. In addition, transporters are sometimes classified by the molecule type that is transported, for example, sugar transporters, chlorine channels, potassium channels, etc. There may be many classes of channels for transporting a single type of molecule (a detailed review of channel types can be found at Alexander, S.P.H. and J.A. Peters: Receptor and transporter nomenclature supplement. Trends Pharmacol. Sci., Elsevier, pp. 65-68 (1997) **[and http://www-biology.ucsd.edu/~msaier/transport/titlepage2.html]**.

Paragraph 2: Ion channels are generally classified by structure and the type of mode of action. For example, extracellular ligand gated channels (ELGs) are comprised of five polypeptide subunits, with each subunit having 4 membrane spanning domains, and are activated by the binding of an extracellular ligand to the channel. In addition, channels are sometimes classified by the ion type that is transported, for example, chlorine channels, potassium channels, etc. There may be many classes of channels for transporting a single type of ion (a detailed review of channel types can be found at Alexander, S.P.H. and J.A. Peters (1997). Receptor and ion channel nomenclature supplement. Trends Pharmacol. Sci., Elsevier, pp. 65-68 **[and http://www-biology.ucsd.edu/~msaier/transport/toc.html]**.

24. (Amended) A process for producing a polypeptide comprising culturing the host cell of claim 9 under conditions sufficient for the production of said polypeptide from a nucleic acid molecule that encodes said polypeptide, and recovering said polypeptide from the host cell culture.

REMARKS

Objection to the Title:

The Examiner has made an objection on the title stating the title is not clearly indicative of the invention. Applicants hereby changed title as set forth above.

Objection to the Drawings:

The drawings objected by the draftsman were corrected.

Objection to the Hyperlinks:

The Examiner objected to the disclosure because it contains an embedded hyperlink and/or other form of browser-executable code. Applicants have deleted the URL's from the specification, as indicated above by the replacement paragraphs.

Rejection under 35 USC §112, 2nd paragraph:

Claims 24, 28 and 29 are rejected as being indefinite because the claims are not clear on how a complementary strand of polynucleotide can produce the polypeptide SEQ ID NO: 2.

Applicants agree with the point that the Examiner raised. However, it is clearly understood that production of a polypeptide such as SEQ ID NO: 2 would be derived from a sense strand of a polynucleotide instead of its complementary strand. The complementary strand would not produce a SEQ ID NO: 2 that required by either claims 24 or 28. Claim 24 is amended to recite that the SEQ ID NO: 2 polypeptide is encoded by a nucleic acid molecule, and claim 28 has a language reciting that a sequence has to be in proper orientation and correct reading frame that a polypeptide comprising SEQ ID NO: 2 is produced. Thus, these claims do point out a specific polynucleotide encoding the polypeptide.

Applicants believe the amendment and the explanation satisfy the requirement under 112, 2nd paragraph. Therefore, the rejection to claims 24, 28 and 29 should be withdrawn.

Rejection under 35 USC §112, 1st paragraph:

Claims 24 and 28 are rejected as being not enabling nucleic acid sequences which are completely complementary to the nucleic acid sequences in claim 4 (a)-(c).

Applicants respectfully disagree. In addition to the SEQ ID NO: 1 and SEQ ID NO: 3 which encode SEQ ID NO: 2, there are several degenerated forms of nucleic acid sequences also encode SEQ ID NO: 2. One of the skilled in the art would known how to generate degenerated form of the nucleic acid sequences from SEQ ID NO: 2 sequence. One of the skilled in the art would do it by using the standard triple codes that translate between nuclei acids and amino acids. Thus, a complete complementary sequence can be predicted basing on the nucleic acid sequences. Therefore, no undue experimentation is required.

Rejection under 35 USC §101 and §112, 1st paragraph:

At page 3 of the Office Action, the Examiner has rejected claims 4, 8, 9, and 24-29 under 35 U.S.C.§101 and §112, 1st paragraph. In summary, the Examiner has stated that the claimed isolated nucleic acid molecules lack a specific and substantial utility or a well-established utility and, consequently, one skilled in the art would not know how to use the claimed invention.

The examiner stated that there is no RNA or protein blot to indicate the expression profile and there is no disclosure of biological role of the protein.

Applicants respectfully disagree. Some of the expression data provided in the figures and in the specification are resulted from a Northern blot analysis. The expression in spleen and breast is not from BLAST hit, but the laboratory performed Northern data (see Figure 1, page 2). The biological roles are disclosed on page 13, for example, the protein of the present invention is related to the family of moncarboxylate transporters (MCTs), which are found on the luminal surface of intestinal and kidney epithelia.

Further, the examiner stated that the homology of a peptide is not reliable indicator for the functional characteristics. However, the study of the protein of the present invention is based on more than a blast homology. Prosite data in Figure 2 show the protein of the present invention has glycosylation site, camp- and cGMP-dependent protein kinase phosphorylation site, PKC phosphorylation site, casein kinase II phosphorylation site, and N-myristorylation site. In addition, that the protein also shows many sites for membrane spanning structure and domain indicates the structure of a transporter protein. Finally, the Hummer search result in Figure 2, page 5 also shows a high statistically significance that the protein of the present invention is a monocarboxylate transporter protein.

On page 6 of the Office Action, the Examiner stated that the claimed invention is incomplete and "real-world" use is not disclosed.

In contrast to the Examiner's assertions, the claimed isolated nucleic acid molecules, such as SEQ ID NOS:1 and 3, that encode a specified amino acid sequence, SEQ ID NO:2, and methods of making and using such nucleic acid molecules have several uses that meet the requirements of 35 U.S.C.§101 and the first paragraph of 35 U.S.C.§112. These, as well as the accepted state of the art view that such molecules have uses within the commercial marketplace in the drug development cycle, since they encode previously unidentified members of important pharmaceutical targets, establishes the utility of the claimed invention.

The utility requirement of a claimed invention requires that an invention must have a specific, substantial and credible utility. These requirements are defined in broad terms in cases such as *Brenner v. Manson,* 148 USPQ 689 (S. Ct. 1966) and the recently adopted Utility Guidelines from the USPTO.

The CCPA in *Nelson v. Bowler*, 206 USPQ 881 (CCPA 1980), clearly accepted a showing of less than a specific therapeutic use of a claimed chemical compound as satisfying the utility requirement.

> *The CCPA held that where a claim does not provide evidence of pharmacological activity of a claimed compound, although it does not establish a specific therapeutic use, manifests a practical utility because knowledge of pharmacological activity is beneficial to the public in that it makes faster and easier for medical researchers to combat illnesses. Nelson v. Bowler, 206 USPQ 881 (CCPA 1980).*

The notion that a recognized valuable addition to even entry points of the drug discovery cycle advances the art sufficient to establish a "usefulness" of a claimed invention should not be ignored. Similar to the *Nelson* case, the present invention, which is drawn to isolated nucleic acid molecules that encode a transporter protein (SEQ ID NO: 2), has useful value in the drug discovery process even though the molecule may not be associated with a specific treatment and/or diagnosis of a particular disease. According to *Nelson*, the present invention provides sufficient knowledge and information that is beneficial to the public, and provides sufficient guidance for researchers to use the claimed subject matter to develop disease treatments and/or diagnostics. It is well recognized that transporters are the most important targets for drug action

(pages 1-15 of the specification). The public disclosure of a new member of this family through the patenting process clearly advances the art and augments the capabilities of biomedical researchers to combat illnesses.

The utility rejection raised by the Examiner also conflicts with the case *Juicy Whip v. Orange Bang* (Fed. Cir. 1999). *Juicy Whip* held that, in order to violate the utility requirement, an invention must be "totally incapable of achieving a useful result." The polypeptides and encoding nucleic acid molecules of the present invention are well known in the art to be valuable drug targets and therefore have readily apparent commercial utilities, such as for screening potential drug compounds, producing antibodies, developing hybridization probes and primers, etc. In addition to the uses disclosed in the specification and discussed herein for the polynucleotides of the present invention, other utilities are readily apparent to one of ordinary skill in the art based on the observed tissue specific expression patterns. Specifically, the proteins/nucleic acid molecules of the present invention are expressed in spleen and breast. Thus, for example, the proteins/nucleic acids of the present invention are commercially useful for developing therapeutic agents for treating diseases affecting these tissues. Therefore, the present invention is not "totally incapable of achieving a useful result." Instead, it is useful.

The specification and figures show that the protein of the present invention has functional domain of monocarboxylate transporter. The disclosure of the function of the transporter is sufficient. Such a function is quite specific for transporter proteins and differentiates them from other proteins. As such, this function is specific enough to define a use for novel transporter proteins and transporter-encoding nucleic acid molecules in the drug discovery process.

As stated in the Background section of the specification(pages 13 –14), members of the transporter protein family, particularly those related to the monocarboxylate transporter subfamily, plays an important role in transporting different substrates, such as L-lactate, pyruvate, and ketone bodies (e.g. acetate, acetoacetate, and beta-hydroxybutyrate) across membranes. Lactate, pyruvate, and other monocarboxylates play critical roles in cellular metabolism and metabolic communication between tissues; essential to these roles is their efficient transport across plasma membranes, which is catalysed by MCTs. In the liver and kidneys, pyruvate and lactate are converted back to glucose via the gluconeogenic pathway. In tissues that use glycolysis as a sources of ATP (for example, cells that have few mitochondria), the end products (such as lactate

and pyruvate) are removed from cells using monocarboyxlate transporters, thereby enabling the continuation of glycolysis and preventing the build-up of toxins.

The protein of the present invention has high homology to MCT3, which is preferentially expressed in the basolateral membranes of retinal pigment epithelium and choroid plexus epithelium. It has been suggested that MCT3 may be important for regulating lactate levels in fluid-bathing neuronal tissues

Novel transporter proteins/nucleic acids are commercially useful for developing therapeutics/diagnostics for these and other pathologies. Thus, there is overwhelming evidence in the art to support the utility of novel transporter proteins and encoding nucleic acid molecules, particularly those related to sugar transporter. Not all nucleic acid molecules, and actually a very limited number, of the 3 billion bases that make up the human genome will encode a protein for these and the other disclosed uses. These uses are quite specific for the transporter family of proteins, even though each member may play a somewhat different role in cellular responses and pathologies. Even though each member may have a somewhat different role in biology and disease, each is a specific composition of matter having substantial, specific and credible uses that the vast majority of other isolated nucleic acid molecules do not possess.

By placing a new member of the transporter protein family into the public domain through the patenting process, the present invention is not only a clear advancement over the prior art (a newly discovered protein/gene) but also enables significant advancement in medicine and further discovery. The Utility requirement cannot be used to contradict the reasons for the patent system, to encourage early disclosures of inventions so that others can benefit from, improve upon, and further develop such inventions. This is particularly important in medicine, wherein early disclosure of key inventions (such as new transporter proteins and encoding nucleic acid molecules) is needed to facilitate the early development of new therapies and diagnostics to treat illnesses.

The grant of a patent to the claimed isolated nucleic acid molecule and the resultant disclosure of the nucleic acid and protein sequences to the public will certainly shorten the process for medical researchers to discover other novel uses for the present transporter-encoding nucleic acids. One example disclosed in the specification is that the present nucleic acid molecules can be used to produce protein targets for identifying agents that bind to the protein targets and modulate protein function. Such agents can be used to precisely determine which

biological and pathological processes the protein is involved in. Furthermore, such agents that bind to a protein target and modulate cell signaling may subsequently be developed and refined for use in mammalian therapeutic applications. All of this later discovery and refinement will be done using the presently claimed material. These uses are clearly commercial and substantial uses that are specific for a very limited number of proteins/nucleic acid molecules.

In addition to serving as targets for developing molecular probes and therapeutic agents, the disclosed uses of the claimed nucleic acid molecules as probes, primers, and chemical intermediates, particularly in biological assays, is sufficient to satisfy the requirements of 35 USC §101 and §112. The claimed invention is directed to nucleic acid sequences that encode a transporter protein with a specified amino acid sequence (SEQ ID NO: 2), such as SEQ ID NOS: 1 and 3. Exemplary uses of the nucleic acid sequences are clearly recited in the specification. Among the examples, the nucleic acid molecules are useful as hybridization probes for messenger RNA molecules, transcript/cDNA molecules, genomic DNA, and variants thereof. An expression vector comprising the nucleic acid sequences can be made that expresses the transporter protein. Such uses are specific for the claimed nucleic acid molecules, and the products of such uses will be clearly different (and hence specific for the claimed molecules) than what would be produced using a different nucleic acid molecule for the same purpose.

In view of law and fact, the utility standard interpreted by the USPTO guidelines is too high. The disclosure of activity of the expressed polynucleotide is not required by any statute or case law interpreting the utility requirement of Section 101, and the enablement requirement of Section 112, first paragraph. The commercial value of a gene that encodes a previously unidentified member of the transporter protein family, members of which are well known in the art to be commercially valuable drug targets, should be sufficient to satisfy the utility requirement.

Conclusions

Claims 4, 8-9, and 24-29 are currently pending.

In view of the above remarks and amendments, Applicants respectfully submit that the application and claims are in condition for allowance, and request that the Examiner reconsider and withdraw the objections and rejections. If for any reason the Examiner finds the application other than in condition for allowance, the Examiner is invited to call the undersigned agent should the Examiner believe a telephone interview would advance prosecution of the application.

Respectfully submitted,

CELERA GENOMICS

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By: _____

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